APPLICATION

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TITLE: EMBOLIZATION

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EMBOLIZATION

TECHNICAL FIELD

The invention relates to embolization, as well as related particles, compositions and methods.

BACKGROUND

Therapeutic vascular occlusions (embolizations) are used to prevent or treat pathological conditions *in situ*. Compositions including embolic particles are used for occluding vessels in a variety of medical applications. Delivery of embolic particles through a catheter is dependent on size uniformity, density and compressibility of the embolic particles.

SUMMARY

The invention relates to embolization, as well as related particles, compositions and methods.

In one aspect, the invention features a substantially spherical porous silica particle having a diameter of from about 100 microns to about 3000 microns.

In another aspect, the invention features a composition that includes a carrier fluid that contains a plurality of substantially spherical porous silica particles. At least some of the plurality of substantially spherical silica particles have a diameter of from about 100 microns to about 3000 microns; and

In a further aspect, the invention features a method that includes administering to a subject a therapeutically effective amount of a composition including a plurality of substantially spherical silica particles in a carrier fluid. At least some of the plurality of substantially spherical silica particles having a diameter of from about 100 microns to about 3000 microns.

Embodiments can include one or more of the following.

In some embodiments, the carrier fluid includes a saline solution.

In certain embodiments, the carrier fluid includes a contrast agent.

In some embodiments, at least some of the substantially spherical porous silica particles have a diameter of at most about 1500 microns.

In certain embodiments, for at least some of the substantially spherical porous silica particles, pores in the substantially spherical porous silica particles have a diameter of from about 20 nanometers to about 90 nanometers.

In some embodiments, for at least some of the substantially spherical porous silica particles, a pore volume of the substantially spherical silica particles is from about 0.4 ml/g to about 1.6 ml/g.

In certain embodiments, the particles can have a pore volume distribution such that about 70% or more of the pore volume of the particles is made up of pores having pore diameters which have a tolerance of about 10 nm or less on the mean pore diameter.

In some embodiments, the particles exhibit a loss of attrition resistance of about 0.1% by weight or less.

In certain embodiments, at least some of the plurality of substantially spherical porous silica particles include one or more therapeutic agents, one or more ferromagnetic materials, one or more MRI visible materials and/or one or more radiopaque materials.

In some embodiments, the plurality of substantially spherical porous silica particles are sterilized.

In some embodiments, the composition is administered to the subject by percutaneous injection.

In certain embodiments, the composition is administered to the subject by a catheter.

In some embodiments, the composition is used to treat a cancer condition. The cancer condition can be, for example, ovarian cancer, colorectal cancer, thyroid cancer, gastrointestinal cancer, breast cancer, prostate cancer and/or lung cancer. Treating the cancer condition can include at least partially occluding a lumen in the subject that provides nutrients to a site of the cancer condition with at least some of the plurality of particles.

In certain embodiments, the method includes at least partially occluding a lumen in the subject with at least some of a plurality of particles.

Embodiments may include one or more of the following advantages.

In some embodiments, the silica particles can be substantially biologically inert and non-degradable in the body.

In certain embodiments, the particles can have, and can maintain after implantation, a highly uniform diameter, geometry, pore volume, and pore size.

In general, the particle diameter, geometry, pore volume and pore diameter can be selected based on a desired application. As an example, in some embodiments (e.g., for embolic applications), the particles may have a spherical geometry with a particle diameter of about 3000 microns or less (e.g., about 1500 microns or less) and a relatively large pore volume, to enhance the suspendability of the particles in a delivery medium such as a contrast agent, and a relatively small pore size to enhance surface uniformity, robustness and abrasion resistance. As another example, in certain embodiments (e.g., for a therapeutic agent delivery applications), pore volume can be selected to contain a desired therapeutic agent volume, and pore size can be selected to produce a desired time release, based on diffusion of therapeutic agent from the pores.

In some embodiments, the particles can be made targetable by incorporation of a magnetic material.

In certain embodiments, the particles can be highly incompressible and exhibit a high crushing strength such that they can withstand contact and delivery through a syringe, catheter or the like, as well as, withstand internal body fluid pressure without fracturing.

Features and advantages are in the description, drawings, and claims.

DESCRIPTION OF DRAWINGS

FIG. 1A is a schematic illustrating uterine artery embolization.

FIG. 1B is a greatly enlarged view of region A of FIG. 1A.

FIG 2 is a cross-sectional view of a silica embolic particle.

FIG 3 is a flow diagram of a method of making silica embolic particles.

Like reference symbols in the various drawings indicate like elements.

DETAILED DESCRIPTION

Referring to FIGS. 1A and 1B, an embolic composition, including embolic particles 111 and a carrier fluid, is injected into a vessel through an instrument such as a catheter 150. Catheter 150 is connected to a syringe barrel 110 with a plunger 160. Catheter 150 is inserted, for example, into a femoral artery 120 of a subject. Catheter 150 delivers the embolic composition to, for example, occlude a uterine artery 130 leading to a fibroid 140. Fibroid 140 is located in the uterus of a female subject. The embolic composition is initially loaded into

syringe 110. Plunger 160 of syringe 110 is then compressed to deliver the embolic composition through catheter 150 into a lumen 165 of uterine artery 130.

FIG. 1B, which is an enlarged view of section 1B of FIG. 1A, shows a uterine artery 130 that is subdivided into smaller uterine vessels 170 (e.g., having a diameter of about two millimeters or less) which feed fibroid 140. The embolic particles 111 in the embolic composition partially or totally fill the lumen of uterine artery 130, either partially or completely occluding the lumen of the uterine artery 130 that feeds uterine fibroid 140.

In general, embolic compositions can be used in, for example, neural, pulmonary, and/or AAA (abdominal aortic aneurysm) applications. The compositions can be used in the treatment of, for example, fibroids, tumors, internal bleeding, arteriovenous malformations (AVMs), and/or hypervascular tumors. The compositions can be used as, for example, fillers for aneurysm sacs, AAA sac (Type II endoleaks), endoleak sealants, arterial sealants, and/or puncture sealants, and/or can be used to provide occlusion of other lumens such as fallopian tubes. Fibroids can include uterine fibroids which grow within the uterine wall (intramural type), on the outside of the uterus (subserosal type), inside the uterine cavity (submucosal type), between the layers of broad ligament supporting the uterus (interligamentous type), attached to another organ (parasitic type), or on a mushroom-like stalk (pedunculated type). Internal bleeding includes gastrointestinal, urinary, renal and varicose bleeding. AVMs are for example, abnormal collections of blood vessels, e.g. in the brain, which shunt blood from a high pressure artery to a low pressure vein, resulting in hypoxia and malnutrition of those regions from which the blood is diverted. In some embodiments, a composition containing the particles can be used to prophylactically treat a condition.

The magnitude of a dose of an embolic composition can vary based on the nature, location and severity of the condition to be treated, as well as the route of administration. A physician treating the condition, disease or disorder can determine an effective amount of embolic composition. An effective amount of embolic composition refers to the amount sufficient to result in amelioration of symptoms or a prolongation of survival of the subject. The embolic compositions can be administered as pharmaceutically acceptable compositions to a subject in any therapeutically acceptable dosage, including those administered to a subject intravenously, subcutaneously, percutaneously, intratrachealy, intramuscularly, intramucosaly, intracutaneously, intra-articularly, orally or parenterally.

An embolic composition can be prepared in calibrated concentrations of the particles for ease of delivery by the physician. Suspensions of the particles in saline solution can be prepared to remain stable (e.g., to not precipitate) over a duration of time. A suspension of the particles can be stable, for example, for from about one minute to about 20 minutes (e.g. from about one minute to about ten minutes, from about two minutes to about seven minutes, from about three minutes to about six minutes). The concentration of particles can be determined by adjusting the weight ratio of the particles to the physiological solution. If the weight ratio of the particles is too small, then too much liquid could be injected into a blood vessel, possibly allowing the particles to stray into lateral vessels. In some embodiments, the physiological solution can contain from about 0.01 weight percent to about 15 weight percent of the particles. A composition can include a mixture of particles, such as particles including one type of surface preferential material and particles including another, different, type of surface preferential material.

In some embodiments, among the particles delivered to a subject in an embolic composition, the majority (e.g., about 50 percent or more, about 60 percent or more, about 70 percent or more, about 80 percent or more, about 90 percent or more) of the particles have a diameter of about 3,000 microns or less (e.g., about 2,500 microns or less; about 2,000 microns or less; about 1,500 microns or less; about 1,200 microns or less; about 900 microns or less; about 700 microns or less; about 500 microns or less; about 400 microns or less; about 300 microns or less; about 100 microns or less) and/or about ten microns or more (e.g., about 100 microns or more; about 300 microns or more; about 400 microns or more; about 500 microns or more; about 700 microns or more; about 900 microns or more; about 1,200 microns or more; about 1,500 microns or more; about 2,000 microns or more; about 2,500 microns or more).

In certain embodiments, the particles delivered to a subject in an embolic composition have a mean diameter of about 3,000 microns or less (e.g., about 2,500 microns or less; about 2,000 microns or less; about 1,500 microns or less; about 1,200 microns or less; about 900 microns or less; about 700 microns or less; about 500 microns or less; about 400 microns or less; about 300 microns or less; about 100 microns or less) and/or about ten microns or more (e.g., about 100 microns or more; about 300 microns or more; about 400 microns or more; about 500 microns or more; about 700 microns or more; about 900 microns or more; about 1,200 microns or more; about 1,500 microns or more; about 2,000 microns or more; about 2,500 microns or

more). Exemplary ranges for the mean diameter of particles delivered to a subject include from about 100 microns to about 500 microns; from about 100 microns to about 300 microns; from about 300 microns to about 500 microns; from about 500 microns to about 700 microns; and from about 900 microns to about 1,200 microns. In general, the particles delivered to a subject in an embolic composition have a mean diameter in approximately the middle of the range of the diameters of the individual particles, and a variance of about 20 percent or less (e.g. about 15 percent or less, about ten percent or less).

In some embodiments, the mean size of the particles delivered to a subject in an embolic composition can vary depending upon the particular condition to be treated. As an example, in embodiments in which the particles in an embolic composition are used to treat a liver tumor, the particles delivered to the subject can have a mean diameter of about 500 microns or less (e.g., from about 100 microns to about 300 microns; from about 300 microns to about 500 microns). As another example, in embodiments in which the particles in an embolic composition are used to treat a uterine fibroid, the particles delivered to the subject in an embolic composition can have a mean diameter of about 1,200 microns or less (e.g., from about 500 microns to about 700 microns; from about 700 microns to about 900 microns; from about 900 microns to about 1,200 microns).

FIG. 2 shows a cross-section of a silica particle 111 having pores 112.

In general, particle 111 is substantially spherical. For example, in some embodiments, particle 111 can have a sphericity of about 0.8 or more (e.g., about 0.85 or more, about 0.9 or more, about 0.95 or more, about 0.97 or more). The sphericity of a particle can be determined using a Beckman Coulter RapidVUE Image Analyzer version 2.06 (Beckman Coulter, Miami, FL). Briefly, the RapidVUE takes an image of continuous-tone (gray-scale) form and converts it to a digital form through the process of sampling and quantization. The system software identifies and measures particles in an image in the form of a fiber, rod or sphere. The sphericity of a particle, which is computed as Da/Dp (where $Da = \sqrt{(4A/\pi)}$; $Dp = P/\pi$; A = pixel area; P = pixel perimeter), is a value from zero to one, with one representing a perfect circle.

In certain embodiments, particle 111 has a diameter of about 3,000 microns or less (e.g., about 2,500 microns or less; about 2,000 microns or less; about 1,500 microns or less; about 1,200 microns or less; about 900 microns or less; about 700 microns or less; about 500 microns or less; about 400 microns or less; about 300 microns or less; about 100 microns or less) and/or

about ten microns or more (e.g., about 100 microns or more; about 300 microns or more; about 400 microns or more; about 500 microns or more; about 700 microns or more; about 900 microns or more; about 1,200 microns or more; about 1,500 microns or more; about 2,000 microns or more; about 2,500 microns or more). Exemplary ranges for the diameter of particle 111 include from about 100 microns to about 500 microns; from about 100 microns to about 300 microns; from about 300 microns to about 500 microns; from about 500 microns to about 700 microns; and from about 900 microns to about 1,200 microns.

In some embodiments, particle 111 has a substantially uniform pore structure. In certain embodiments, particle 111 has non-uniform pore structure.

In certain embodiments, pores 112 can interconnect throughout particle 111. In some embodiments, pores 112 do not interconnect throughout particle 111.

In some embodiments, the diameters of pores 112 in particle 111 are about 20 nanometers or more (e.g., about 30 nanometers or more, about 40 nanometers or more) and/or about 90 nanometers or less (e.g., about 80 nanometers or less, about 70 nanometers or less, about 60 nanometers or less).

In general, the density of particle 111 (e.g., as measured in grams of material per unit volume) is such that it can be readily suspended in a carrier fluid (e.g., a pharmaceutically acceptable carrier, such as a saline solution, a contrast solution, or a mixture thereof) and remain suspended during delivery (e.g., to form a composition, such as an embolization composition). In some embodiments, the density of particle 111 is from about 1.1 grams per cubic centimeter to about 1.4 grams per cubic centimeter. As an example, for suspension in a saline-contrast solution, the density of particle 111 can be from about 1.2 grams per cubic centimeter to about 1.3 grams per cubic centimeter.

In some embodiments, particle 111 can have a high pore diameter and/or a high pore volume uniformity. For example, particle 111 can have a pore diameter distribution such that about 70% or more of the pore volume is made up pores having pore diameters which have a tolerance of not more than 10 nanometers on the mean pore diameter. Pore volume and diameter can be measured by mercury porosimetry.

In certain embodiments, particle 111 can exhibit good resistance to abrasion. For example, a particle can exhibit no detectable loss in attrition resistance. In some embodiments, the loss of attrition of particle 111, as measured using a standard attrition test according to the

Peter Spence method, is about 0.1 weight percent or less (e.g., about 0.05 weight percent or less).

In some embodiments, particle 111 can exhibit high crush strength.

Characterization of silica particles is disclosed, for example, in U.S. Patent No. 4,640,807 and European Patent No. 067459, both of which are hereby incorporated by reference.

In some embodiments, particle 111 can include one or more therapeutic agents (e.g., drugs). The therapeutic agent can be in and/or on particle 111. For example, pores 112 of particle 111 can include a therapeutic agent.

Therapeutic agents include agents that are negatively charged, positively charged, amphoteric, or neutral. Therapeutic agents can be, for example, materials that are biologically active to treat physiological conditions; pharmaceutically active compounds; gene therapies; nucleic acids with and without carrier vectors; oligonucleotides; gene/vector systems; DNA chimeras; compacting agents (e.g., DNA compacting agents); viruses; polymers; hyaluronic acid; proteins (e.g., enzymes such as ribozymes); cells (of human origin, from an animal source, or genetically engineered); stem cells; immunologic species; nonsteroidal anti-inflammatory medications; oral contraceptives; progestins; gonadotrophin-releasing hormone agonists; chemotherapeutic agents; and radioactive species (e.g., radioisotopes, radioactive molecules). Non-limiting examples of therapeutic agents include anti-thrombogenic agents; antioxidants; angiogenic and anti-angiogenic agents and factors; anti-proliferative agents (e.g., agents capable of blocking smooth muscle cell proliferation); anti-inflammatory agents; calcium entry blockers; antineoplastic/antiproliferative/anti-mitotic agents (e.g., paclitaxel, doxorubicin, cisplatin); antimicrobials; anesthetic agents; anti-coagulants; vascular cell growth promoters; vascular cell growth inhibitors; cholesterol-lowering agents; vasodilating agents; agents which interfere with endogenous vasoactive mechanisms; and survival genes which protect against cell death. Therapeutic agents are described, for example, in co-pending U.S. Patent Application No. 10/615,276, filed on July 8, 2003, and entitled "Agent Delivery Particle", which is incorporated herein by reference.

Referring to FIG. 3, particles 111 can be prepared by adaptation of processes described in U.S. Patent No. 4,640,807 and European Patent No. 067459. In step 300, a silica hydrosol mix is prepared by thorough mixing of an alkali metal silicate and an acid. Next, in step 310, the silica hydrosol is converted to hydrogel particles by dropping the hydrosol mix through a water-immiscible liquid into an aqueous solution. Controlling the break-up of the hydrosol stream

enables control of size (e.g., diameter) and shape of the resulting particles. Next, in step 320, the hydrogel particles are partially dried in humid air with temperatures, for example, above 100 °C, wherein a controlled amount of water is removed from the particles. The amount of water removed from the particles can be varied, enabling control of the pore volume of the resulting particles. Further, partial drying can reduce (e.g., prevent) formation of cracks resulting in increased crushing strength. A high crushing strength can enable particles 111 to withstand contact and delivery through a syringe, catheter, or the like, as well as, withstand internal body fluid pressure without fracturing. Partial drying in the presence of humid air can yield particles with a narrow distribution of size (i.e., diameter of particles). Next, in step 330, the particles are subjected to hydrothermal treatment (a treatment at elevated temperatures with liquid water and/or water vapor). The hydrothermal treatment yields particles with a narrow distribution of pore diameter. Next, in step 340, the cation content of the hydrogel particles is lowered by removing alkali metals. Finally, in step 350, the particles are dried, at temperatures, for example, about 200 °C, and optionally calcined. The particles can be sterilized by e.g., heat or radiation treatment, and suspended in a suitable carrier, e.g., saline and/or a contrast solution such as, Omnipaque 300 (Nycomed, Buckinghamshire, UK. Omnipaque is an aqueous solution of Iohexol, N.N.-Bis (2,3-dihydroxypropyl)-T-[N-(2,3-dihydroxypropyl)-acetamide]-2,4,6-trilodo-isophthalamide; Omnipaque 300 contains 647 mg of iohexol equivalent to 300 mg of organic iodine per ml).

The particle diameter, pore diameter and volume and/or uniformity can be controlled to produce particles optimized for a particular application. For example, for a therapeutic delivery application, particle diameter and pore volume can be selected to contain a desired amount of therapeutic agent. The pore diameter can be selected to elute the therapeutic agent into the body based on diffusion processes at a desired rate. A composition including a mixture of particles having known percentages of particles with different particle diameters, pore diameter and pore volume can be prepared to produce a desired dosage profile. Particles of different diameters and pore characteristics can also include different therapeutic agent s. The therapeutic agent delivery particles can be implanted into a lumen, e.g., a vascular lumen by catheterization, e.g., as embolic particles, or injected into soft tissue adjacent a cancerous tumor or other lesion.

While certain embodiments have been described, the invention is not so limited.

As an example, in some embodiments a particle can be coated (e.g., with a bioabsorbable material, such as sodium alginate). The coating can contain, for example, one or more therapeutic agents. In some cases, the coating can be, for example, a degradable and/or bioabsorbable polymer which erodes when the particle is administered. The coating can assist in controlling the rate at which therapeutic agent is released from the particle (e.g., from the surface preferential material). For example, the coating can be in the form of a porous membrane. The coating can delay an initial burst of therapeutic agent release. The coating can be applied by dipping or spraying the particle. The erodible polymer can be a polysaccharide (such as an alginate) or a polysaccharide derivative. In some embodiments, the coating can be an inorganic, ionic salt. Other erodible coatings include water soluble polymers (such as polyvinyl alcohol, e.g., that has not been cross-linked), biodegradable poly DL-lactide-poly ethylene glycol (PELA), hydrogels (e.g., polyacrylic acid, haluronic acid, gelatin, carboxymethyl cellulose), polyethylene glycols (PEG), chitosan, polyesters (e.g., polycaprolactones), and poly(lactic-co-glycolic) acids (e.g., poly(d-lactic-co-glycolic) acids). The coating can include therapeutic agent or can be substantially free of therapeutic agent. The therapeutic agent in the coating can be the same as or different from an agent on a surface layer of the particle. A polymer coating, e.g. an erodible coating, can be applied to the particle surface in cases in which a high concentration of therapeutic agent has not been applied to the particle surface. Coatings are described, for example, in U.S. Patent Application No. 10/615,276, filed on July 8, 2003, and entitled "Agent Delivery Particle", which is incorporated herein by reference.

As an additional example, in some embodiments one or more particles is/are substantially nonspherical. In some embodiments, particles can be shaped (e.g., molded, compressed, punched, and/or agglomerated with other particles) at different points in the particle manufacturing process. Shaped particles are described, for example, in Bourne et al., U.S. Published Patent Application No. US 2003/0203985 A1, which is incorporated herein by reference.

As a further example, in some embodiments the particles can be used for tissue bulking. As an example, the particles can be placed (e.g., injected) into tissue adjacent to a body passageway. The particles can narrow the passageway, thereby providing bulk and allowing the tissue to constrict the passageway more easily. The particles can be placed in the tissue according to a number of different methods, for example, percutaneously, laparoscopically,

and/or through a catheter. In certain embodiments, a cavity can be formed in the tissue, and the particles can be placed in the cavity. Particle tissue bulking can be used to treat, for example, intrinsic sphincteric deficiency (ISD), vesicoureteral reflux, gastroesophageal reflux disease (GERD), and/or vocal cord paralysis (e.g., to restore glottic competence in cases of paralytic dysphonia). In some embodiments, particle tissue bulking can be used to treat urinary incontinence and/or fecal incontinence. The particles can be used as a graft material or a filler to fill and/or to smooth out soft tissue defects, such as for reconstructive or cosmetic applications (e.g., surgery). Examples of soft tissue defect applications include cleft lips, scars (e.g., depressed scars from chicken pox or acne scars), indentations resulting from liposuction, wrinkles (e.g., glabella frown wrinkles), and soft tissue augmentation of thin lips. Tissue bulking is described, for example, in Bourne et al., U.S. Published Patent Application No. US 2003/0233150 A1, which is incorporated herein by reference.

As another example, the particles can include (e.g., encapsulate) diagnostic agent(s) such as a radiopaque material, an MRI-visible material, a ferromagnetic material, and/or an ultrasound contrast agent. For example, a silica particle can encapsulate a ferromagnetic material so that the position of the particle in a lumen can be manipulated with a magnetic field. The magnetic field can be created outside the subject or inside the subject (e.g., via a magnetic catheter). In some embodiments, a ferromagnetic material can be incorporated into silica particles by adding the magnetic material to the silica hydrosol mix (step 300, FIG. 3) and forming particles as illustrated in FIG. 3. Particles containing diagnostic agents are described in U.S. Patent Application Serial No. 10/651,475, filed on August 29, 2003, and entitled "Embolization", and magnetic devices are described in U.S. Patent Application No. 10/108,874, filed on March 29, 2002, and entitled "Magnetically Enhanced Injection Catheter", both of which are incorporated herein by reference.

As yet another example, in certain embodiments, a particle can include one or more therapeutic agents (e.g., in the pores of the particle) and one or more diagnostic agents (e.g., one or more ferromagnetic materials encapsulated in the silica). In certain embodiments, a therapeutic agent can be conjugated with a diagnostic agent. Including both therapeutic agent(s) and diagnostic agent(s) in a particle can enhance the ability to deliver the therapeutic agent in a targeted way.

As a further example, in some embodiments a particle contains materials in addition to silica. For example, in some embodiments, the particle can include one or more polymeric materials (e.g., matrix polymeric materials). Examples of polymeric materials include polyvinyl alcohols, polyacrylic acids, polymethacrylic acids, poly vinyl sulfonates, carboxymethyl celluloses, hydroxyethyl celluloses, substituted celluloses, polyacrylamides, polyethylene glycols, polyamides, polyureas, polyurethanes, polyesters, polyethers, polystyrenes, polysaccharides, polylactic acids, polyethylenes, polymethylmethacrylates, polycaprolactones, polyglycolic acids, poly(lactic-co-glycolic) acids (e.g., poly(d-lactic-co-glycolic) acids), and copolymers or mixtures thereof. In some embodiments, the polymer can be substantially formed of a highly water insoluble, high molecular weight polymer. An example of such a polymer is a high molecular weight polyvinyl alcohol (PVA) that has been acetalized. A polymer can be substantially pure intrachain 1,3-acetalized PVA and substantially free of animal derived residue such as collagen. Examples of particles containing such materials are disclosed in U.S. Patent Application Serial No. 10/637,130, filed August 8, 2003, and entitled "Embolization", which is hereby incorporated by reference.

As an additional example, in some embodiments, a particle can be shaped, such as described, for example, in U.S. Patent Application No. 10/700,970, filed on November 4, 2003, and entitled "Embolization", and U.S. Patent Application No. 10/700,403 filed on November 4, 2003, and entitled "Embolization", both of which are incorporated herein by reference.

As another example, in some embodiments a particle can be formed with no pores and/or no cavities.

Other embodiments are in the claims.